Docket No.: NY-HUBR 1189-US (10104500)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Peter Sondermann, et al

Application No.: 09/856,933

Group Art Unit: 1644

Filed: February 27, 2002

Examiner: M. A. Belyavskyi

For: RECOMBINANT SOLUBLE Fc RECEPTORS

Commissioner for Patents
P. O. Box 1450
Alexandria, Va. 22313-1450

DECLARATION

The UNDERSIGNED hereby declares as follows:

1. I am one of the correctly named co-inventors of the referenced application, and am fully familiar with the application and its prosecution.

2. I have conducted (or participated in) experiments that demonstrate that pharmaceutical compositions containing a recombinant soluble FcγRIIb receptor, wherein the receptor contains the amino acid sequence of SEQ ID NO: 3, can be used to treat autoimmune diseases, allergies or tumor diseases. 24th January 2005

3. DBA/1 mice with experimental allergic encephalomyelitis (EAE) are an accepted animal model for multiple sclerosis (MS). EAE is induced in the mice by immunization with myelin oligodendrocyte glycoprotein (MOG), which results in MS-like symptoms (e.g., paralytic symptoms, brain lesions). Thirty DBA/1 mice were immunized with MOG to induce EAE and were then treated (in groups of ten) at 48 hour intervals with either PBS (control 1), 100 μg trp-synthase from E. coli (control 2) or 100 μg soluble FcγRIIb receptor. Symptoms of EAE were individually evaluated and the disease index was calculated for each mouse in accordance with Abdul-Majid, et al., *J. Neuroimmunol.* 111:23-33 (2000). The disease index was considerably lower when FcγRIIb was administered as compared to both controls.

4. NZBW/F_1 mice represent an accepted animal model for systemic lupus erythematosus (SLE) (See Theofilopoulos and Dixon, *Adv. Immunol.* 37: 269-390 (1985)). Groups of ten NZBW/F_1 mice each were treated subcutaneously with either PBS (control group) or 100 μg soluble FcγRIIb receptor at weekly intervals. The results showed that the survival rate was considerably increased by administering FcγRIIb compared to the control. After

40 weeks, all mice treated with FcγRIIb were alive. However, 70% of the control group had died after this time period.

5. An important criterion in analyzing progression of SLE is proteinuria of the diseased NZBW/F_1 mice, which occurs as a result of developing glomerulonephritis. The proteinuria of the mice treated as described in 4, *supra*, was determined. The results indicate that administration of FcγRIIb considerably slowed the increase in proteinuria as compared to the control group.

6. An accepted animal model for rheumatoid arthritis is adjuvant-induced arthritis (AIA) in mice. The inflammatory reaction is caused by administering an antigen into a joint. Treatment of these mice was carried out by administering either 100 µg soluble FcγRIIb receptor or a control, intraperitoneally at weekly intervals in accordance with Waksman, *J. Immunol.* 56(1): 12-34 (2002) and Holmdahl, et al., *Immunol. Rev.*, 184: 184-202 (2001). The arthritis index was calculated as [joint diameter of arthritic knee joint (mm) divided by joint diameter of contralateral knee joint (mm)] multiplied by 100. Administration of FcγRIIb significantly decreased the arthritis index in the mice as compared to the control.

7. Immune complex (IC) –induced alveolitis in mice represents an accepted animal model for inflammatory diseases that are associated with a high immune complex burden. In order to induce the disease, mice were injected intraperitoneally with an antigen and intratracheally with an antibody directed against the antigen. This caused the formation of immune complexes in the lung that result in inflammatory reactions. Hemorrhaging and the infiltration of neutrophils (PMN) were evaluated. 100 µg FcγRIIb was simultaneously administered intraperitoneally in accordance with Tanoue, et al., *Int. Arch Allergy Immunol.* 101(1): 47-51 (1993) and Yoshizawa, et al., *Clin, Immunol. Immunpathol.* 61(3): 376-386 (1991). Administration of FcγRIIb almost completely suppressed the inflammatory reactions and also reduced hemorrhage.

8. The results of these experiments show that FcγRIIb, containing the amino acid sequence of SEQ ID NO: 3, has a clear positive effect on the course of diseases in which immune complexes are involved, in particular autoimmune diseases.

9. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information or belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements and the like so made may jeopardize the validity of this declaration, the subject application, or any patent issued thereon.

Dated: 24/01/05

By Uwe
Dr. Uwe Jacob